## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use CERVARIX safely and effectively. See full prescribing information for CERVARIX.**

**CERVARIX [Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant]**
**Suspension for Intramuscular Injection**
**Initial U.S. Approval: 2009**

### INDICATIONS AND USAGE

CERVARIX is a vaccine indicated for the prevention of the following diseases caused by oncogenic human papillomavirus (HPV) types 16 and 18:

- cervical cancer,
- cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma *in situ*, and
- cervical intraepithelial neoplasia (CIN) grade 1. (1.1)

CERVARIX is approved for use in females 10 through 25 years of age.
Limitations of Use and Effectiveness (1.2)

- CERVARIX does not provide protection against disease due to all HPV types. (14.3)
- CERVARIX has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a woman has previously been exposed through sexual activity. (14.2)

### DOSAGE AND ADMINISTRATION

Three doses (0.5-mL each) by intramuscular injection according to the following schedule: 0, 1, and 6 months. (2.2)

### DOSAGE FORMS AND STRENGTHS

0.5-mL suspension for injection as a single-dose vial or pre-filled syringe. (3)

### CONTRAINDICATIONS

Severe allergic reactions (e.g., anaphylaxis) to any component of CERVARIX. (4)

### WARNINGS AND PRECAUTIONS

- Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with CERVARIX. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position. (5.1)
- Do not use the prefilled syringes in latex sensitive individuals. (5.2)

### ADVERSE REACTIONS

- Most common local adverse reactions in ≥20% of subjects were pain, redness, and swelling at the injection site. (6.1)
- Most common general adverse events in ≥20% of subjects were fatigue, headache, myalgia, gastrointestinal symptoms, and arthralgia. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov**

**To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**

### DRUG INTERACTIONS

Do not mix CERVARIX with any other vaccine in the same syringe or vial. (7.1)

### USE IN SPECIFIC POPULATIONS

- Safety has not been established in pregnant women. Register women who receive CERVARIX while pregnant in the pregnancy registry by calling 1-888-452-9622. (8.1)
- Immunocompromised individuals may have a reduced immune response to CERVARIX. (8.6)

**Revised: October 2009**
**CRX:1PI**

**See 17 for PATIENT COUNSELING INFORMATION**

**Revised: 11/2009**

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**FULL PRESCRIBING INFORMATION: CONTENTS ***



*** Sections or subsections omitted from the full prescribing information are not listed**

## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

### 1.1 Indications

CERVARIX® is indicated for the prevention of the following diseases caused by oncogenic human papillomavirus (HPV) types 16 and 18 *[see Clinical Studies (14)]:*

- cervical cancer,
- cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma *in situ*, and
- cervical intraepithelial neoplasia (CIN) grade 1.

CERVARIX is approved for use in females 10 through 25 years of age.

### 1.2 Limitations of Use and Effectiveness

CERVARIX does not provide protection against disease due to all HPV types *[see Clinical Studies (14.3)]*.
CERVARIX has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a woman has previously been exposed through sexual activity *[see Clinical Studies (14.2)]*.
Females should continue to adhere to recommended cervical cancer screening procedures *[see Patient Counseling Information (17)]*.
Vaccination with CERVARIX may not result in protection in all vaccine recipients.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Preparation for Administration

Shake vial or syringe well before withdrawal and use. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. CERVARIX also should be inspected visually for cracks in the vial or syringe prior to administration. If any of these conditions exist, the vaccine should not be administered. With thorough agitation, CERVARIX is a homogeneous, turbid, white suspension. Discard if it appears otherwise.

### 2.2 Dose and Schedule

Immunization with CERVARIX consists of 3 doses of 0.5-mL each, by intramuscular injection according to the following schedule: 0, 1, and 6 months. The preferred site of administration is the deltoid region of the upper arm.
Do not administer this product intravenously, intradermally, or subcutaneously.

## 3 DOSAGE FORMS AND STRENGTHS

CERVARIX is a suspension for intramuscular injection available in 0.5-mL single-dose vials and prefilled TIP-LOK® syringes.

## 4 CONTRAINDICATIONS

Severe allergic reactions (e.g., anaphylaxis) to any component of CERVARIX *[see Description (11)]*.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Syncope

Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with CERVARIX. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

### 5.2 Latex

The tip cap and the rubber plunger of the needleless prefilled syringes contain dry natural latex rubber that may cause allergic reactions in latex sensitive individuals. The vial stopper does not contain latex.

### 5.3 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the immunization history for possible vaccine hypersensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks. Appropriate medical treatment and supervision should be readily available in case of anaphylactic reactions following administration of CERVARIX.

## 6 ADVERSE REACTIONS

The most common local adverse reactions (≥20% of subjects) were pain, redness, and swelling at the injection site.

The most common general adverse events (≥20% of subjects) were fatigue, headache, myalgia, gastrointestinal symptoms, and arthralgia.

**6.1 Clinical Studies Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice. There is the possibility that broad use of CERVARIX could reveal adverse reactions not observed in clinical trials.

Studies in Females 10 Through 25 Years of Age: The safety of CERVARIX was evaluated by pooling data from controlled and uncontrolled clinical trials involving 23,713 females 10 through 25 years of age in the pre-licensure clinical development program. In these studies, 12,785 females (10 through 25 years of age) received at least one dose of CERVARIX and 10,928 females received at least one dose of a control [Hepatitis A Vaccine containing 360 EL.U. (10 through 14 years of age), Hepatitis A Vaccine containing 720 EL.U. (15 through 25 years of age), or $Al(OH)_3$ (500 mcg, 15 through 25 years of age)].

Data on solicited local and general adverse events were collected by subjects or parents using standardized diary cards for 7 consecutive days following each vaccine dose (i.e., day of vaccination and the next 6 days). Unsolicited adverse events were recorded with diary cards for 30 days following each vaccination (day of vaccination and 29 subsequent days). Parents and/or subjects were also asked at each study visit about the occurrence of any adverse events and instructed to immediately report serious adverse events throughout the study period. These studies were conducted in North America, Latin America, Europe, Asia, and Australia. Overall, the majority of subjects were white (59%), followed by Asian (26%), Hispanic (9%), black (3%), and other racial/ethnic groups (3%).

*Solicited Adverse Events:* The reported frequencies of solicited local injection site reactions (pain, redness, and swelling) and general adverse events (fatigue, fever, gastrointestinal symptoms, headache, arthralgia, myalgia, and urticaria) within 7 days after vaccination in females 10 through 25 years of age are presented in Table 1. An analysis of solicited local injection site reactions by dose is presented in Table 2. Local reactions were reported more frequently with CERVARIX when compared with the control groups; in ≥84% of recipients of CERVARIX, these local reactions were mild to moderate in intensity. Compared with dose 1, pain was reported less frequently after doses 2 and 3 of CERVARIX, in contrast to redness and swelling where there was a small increased incidence. There was no increase in the frequency of general adverse events with successive doses.

Table 1. Rates of Solicited Local Adverse Reactions and General Adverse Events in Females 10 Through 25 Years of Age Within 7 Days of Vaccination (Total Vaccinated Cohort[a])

| **Adverse Reaction/Event** | **CERVARIX (10-25 yrs) %** | **HAV 720[b] (15-25 yrs) %** | **HAV 360[c] (10-14 yrs) %** | **$Al(OH)_3$ Control[d] (15-25 yrs) %** |
|---|---|---|---|---|
| **Local Adverse Reaction** | **N = 6,431** | **N = 3,079** | **N = 1,027** | **N = 549** |
| Pain | 91.8 | 78.0 | 64.2 | 87.2 |
| Redness | 48.0 | 27.6 | 25.2 | 24.4 |
| Swelling | 44.1 | 19.8 | 17.3 | 21.3 |
| **General Adverse Event** | **N = 6,432** | **N = 3,079** | **N = 1,027** | **N = 549** |
| Fatigue | 55.0 | 53.7 | 42.3 | 53.6 |
| Headache | 53.4 | 51.3 | 45.2 | 61.4 |
| GI[e] | 27.8 | 27.3 | 24.6 | 32.8 |
| Fever (≥99.5°F) | 12.8 | 10.9 | 16.0 | 13.5 |
| Rash | 9.6 | 8.4 | 6.7 | 10.0 |
| | **N = 5,881** | **N = 3,079** | **N = 1,027** | **—** |
| Myalgia[f] | 49.1 | 44.9 | 33.1 | — |
| Arthralgia[f] | 20.8 | 17.9 | 19.9 | — |
| Urticaria[f] | 7.4 | 7.9 | 5.4 | — |

[a]Total vaccinated cohort included subjects with at least one documented dose (N).

[b]HAV 720 = Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 mcg $Al(OH)_3$].

[c]HAV 360 = Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 mcg of $Al(OH)_3$].

[d]$Al(OH)_3$ Control = control containing 500 mcg $Al(OH)_3$.

[e]GI = Gastrointestinal symptoms, including nausea, vomiting, diarrhea, and/or abdominal pain.

[f]Adverse events solicited in a subset of subjects.

Table 2. Rates of Solicited Local Adverse Reactions in Females 10 Through 25 Years of Age by Dose Within 7 Days of Vaccination (Total Vaccinated Cohort[a])

| Adverse Reaction | CERVARIX (10-25 yrs) % | | | HAV 720[b] (15-25 yrs) % | | | HAV 360[c] (10-14 yrs) % | | | $Al(OH)_3$ Control[d] (15-25 yrs) % | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Post-Dose | | | Post-Dose | | | Post-Dose | | | Post-Dose | | |
| | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| **N** | **6,415** | **6,197** | **5,936** | **3,070** | **2,919** | **2,758** | **1,027** | **1,021** | **1,011** | **546** | **521** | **500** |
| Pain | 86.9 | 76.2 | 78.7 | 65.6 | 54.4 | 56.1 | 48.5 | 38.5 | 36.9 | 79.1 | 66.8 | 72.4 |
| Pain, Grade 3[e] | 7.5 | 5.7 | 7.7 | 2.0 | 1.4 | 2.0 | 0.8 | 0.2 | 1.6 | 9.0 | 6.0 | 8.6 |
| Redness | 27.8 | 29.6 | 35.6 | 16.6 | 15.2 | 16.1 | 15.6 | 13.3 | 12.1 | 11.5 | 11.5 | 15.6 |
| Redness, >50 mm | 0.2 | 0.5 | 1.0 | 0.1 | 0.1 | 0.0 | 0.1 | 0.2 | 0.1 | 0.2 | 0.0 | 0.0 |
| Swelling | 22.7 | 25.2 | 32.7 | 10.5 | 9.4 | 10.5 | 9.4 | 8.6 | 7.6 | 10.3 | 10.4 | 12.0 |
| Swelling, >50 mm | 1.2 | 1.0 | 1.3 | 0.2 | 0.2 | 0.2 | 0.4 | 0.3 | 0.0 | 0.0 | 0.0 | 0.0 |

[a]Total vaccinated cohort included subjects with at least one documented dose (N).

[b]HAV 720 = Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 mcg $Al(OH)_3$].

[c]HAV 360 = Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 mcg of $Al(OH)_3$].

[d]$Al(OH)_3$ Control = control containing 500 mcg $Al(OH)_3$.

[e]Defined as spontaneously painful or pain that prevented normal daily activities.

The pattern of solicited local adverse reactions and general adverse events following administration of CERVARIX was similar between the age cohorts (10 through 14 years and 15 through 25 years).

*Unsolicited Adverse Events:* The frequency of unsolicited adverse events that occurred within 30 days of vaccination (≥1% for CERVARIX and greater than any of the control groups) in females 10 through 25 years of age are presented in Table 3.

Table 3. Rates of Unsolicited Adverse Events in Females 10 Through 25 Years of Age Within 30 Days of Vaccination (≥1% For CERVARIX and Greater Than HAV 720, HAV 360, or $Al(OH)_3$ Control) (Total Vaccinated Cohort[a])

| Adverse Event | CERVARIX % (N = 6,654) | HAV 720[b] % (N = 3,186) | HAV 360[c] % (N = 1,032) | $Al(OH)_3$ Control[d] % (N = 581) |
|---|---|---|---|---|
| Headache | 5.3 | 7.6 | 3.3 | 9.3 |
| Nasopharyngitis | 3.6 | 3.4 | 5.9 | 3.3 |
| Influenza | 3.2 | 5.6 | 1.3 | 1.9 |
| Pharyngolaryngeal pain | 2.9 | 2.7 | 2.2 | 2.2 |
| Dizziness | 2.2 | 2.6 | 1.5 | 3.1 |
| Upper respiratory infection | 2.0 | 1.3 | 6.7 | 1.5 |
| Chlamydia infection | 2.0 | 4.4 | 0.0 | 0.0 |
| Dysmenorrhea | 2.0 | 2.3 | 1.9 | 4.0 |
| Pharyngitis | 1.5 | 1.8 | 2.2 | 0.5 |
| Injection site bruising | 1.4 | 1.8 | 0.7 | 1.5 |
| Vaginal infection | 1.4 | 2.2 | 0.1 | 0.9 |
| Injection site pruritus | 1.3 | 0.5 | 0.6 | 0.2 |
| Back pain | 1.1 | 1.3 | 0.7 | 3.1 |
| Urinary tract infection | 1.0 | 1.4 | 0.3 | 1.2 |

[a]Total vaccinated cohort included subjects with at least one dose administered (N).

[b]HAV 720 = Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 mcg $Al(OH)_3$].

[c]HAV 360 = Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 mcg of $Al(OH)_3$].

[d]$Al(OH)_3$ Control = control containing 500 mcg $Al(OH)_3$.

*New Onset Autoimmune Diseases (NOADs):* The pooled safety database, which included controlled and uncontrolled trials which enrolled females 10 through 25 years of age, was searched for new medical conditions indicative of potential new onset autoimmune diseases. Overall, the incidence of potential NOADs, as well as NOADs, in the group receiving CERVARIX was 0.8% (95/12,533) and comparable to the pooled control group (0.8%, 87/10,730) during the 4.3 years of follow-up (mean 3.0 years) (Table 4).
In the largest randomized, controlled trial (Study 2) which enrolled females 15 through 25 years of age and which included active surveillance for potential NOADs, the incidence of potential NOADs and NOADs was 0.8% among subjects who received CERVARIX (78/9,319) and 0.8% among subjects who received Hepatitis A Vaccine [720 EL.U. of antigen and 500 mcg $Al(OH)_3$] control (77/9,325).

Table 4. Incidence of New Medical Conditions Indicative of Potential New Onset Autoimmune Disease and New Onset Autoimmune Disease Throughout the Follow-up Period Regardless of Causality in Females 10 Through 25 Years of Age (Total Vaccinated Cohort[a])

| | **CERVARIX (N = 12,533)** | **Pooled Control Group[b] (N = 10,730)** |
|---|---|---|
| | **n (%)[c]** | **n (%)[c]** |
| **Total Number of Subjects With at Least One Medical Condition** | 95 (0.8) | 87 (0.8) |
| Arthritis[d] | 9 (0.0) | 4 (0.0) |
| Celiac disease | 2 (0.0) | 5 (0.0) |
| Dermatomyositis | 0 (0.0) | 1 (0.0) |
| Diabetes mellitus insulin-dependent (Type 1 or unspecified) | 5 (0.0) | 5 (0.0) |
| Erythema nodosum | 3 (0.0) | 0 (0.0) |
| Hyperthyroidism[e] | 14 (0.1) | 15 (0.1) |
| Hypothyroidism[f] | 30 (0.2) | 28 (0.3) |
| Inflammatory bowel disease[g] | 8 (0.1) | 4 (0.0) |
| Multiple sclerosis | 4 (0.0) | 1 (0.0) |
| Myelitis transverse | 1 (0.0) | 0 (0.0) |
| Optic neuritis/Optic neuritis retrobulbar | 3 (0.0) | 1 (0.0) |
| Psoriasis[h] | 8 (0.1) | 11 (0.1) |
| Raynaud’s phenomenon | 0 (0.0) | 1 (0.0) |
| Rheumatoid arthritis | 4 (0.0) | 3 (0.0) |
| Systemic lupus erythematosus[i] | 2 (0.0) | 3 (0.0) |
| Thrombocytopenia[j] | 1 (0.0) | 1 (0.0) |
| Vasculitis[k] | 1 (0.0) | 3 (0.0) |
| Vitiligo | 2 (0.0) | 2 (0.0) |

[a]Total vaccinated cohort included subjects with at least one documented dose (N).

[b]Pooled Control Group = Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 mcg $Al(OH)_3$], Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 mcg of $Al(OH)_3$], and a control containing 500 mcg $Al(OH)_3$.

[c]n (%): number and percentage of subjects with medical condition.

[d]Term includes reactive arthritis and arthritis.

[e]Term includes Basedow's disease, goiter, and hyperthyroidism.

[f]Term includes thyroiditis, autoimmune thyroiditis, and hypothyroidism.

[g]Term includes colitis ulcerative, Crohn's disease, proctitis ulcerative, and inflammatory bowel disease.

[h]Term includes psoriatic arthropathy, nail psoriasis, guttate psoriasis, and psoriasis.

[i]Term includes systemic lupus erythematosus and cutaneous lupus erythematosus.

[j]Term includes idiopathic thrombocytopenic purpura and thrombocytopenia.

[k]Term includes leukocytoclastic vasculitis and vasculitis.

Serious Adverse Events: In the pooled safety database, inclusive of controlled and uncontrolled studies, which enrolled females 10 through 72 years of age, 5.3% (862/16,142) of subjects who received CERVARIX and 5.9% (814/13,811) of subjects who received control reported at least one serious adverse event, without regard to causality, during the entire follow-up period (up to 7.4 years). Among females 10 through 25 years of age enrolled in these clinical studies, 6.4% of subjects who received CERVARIX and 7.2% of subjects who received the control reported at least one serious adverse event during the entire follow-up period (up to 7.4 years).

Deaths: In completed and ongoing studies which enrolled 57,323 females 9 through 72 years of age, 37 deaths were reported during the 7.4 years of follow-up: 20 in subjects who received CERVARIX (0.06%, 20/33,623) and 17 in subjects who received control (0.07%, 17/23,700). Causes of death among subjects were consistent with those reported in adolescent and adult female populations. The most common causes of death were motor vehicle accident (5 subjects who received CERVARIX; 5 subjects who received control) and suicide (2 subjects who received CERVARIX; 5 subjects who received control), followed by neoplasm (3 subjects who received CERVARIX; 2 subjects who received control), autoimmune disease (3 subjects who received CERVARIX; 1 subject who received control), infectious disease (3 subjects who received CERVARIX; 1 subject who received control), homicide (2 subjects who received CERVARIX; 1 subject who received control), cardiovascular disorders (2 subjects who received CERVARIX), and death of unknown cause (2 subjects who received control). Among females 10 through 25 years of age, 31 deaths were reported (0.05%, 16/29,467 of subjects who received CERVARIX and 0.07%, 15/20,192 of subjects who received control.

### 6.2 Postmarketing Experience

In addition to reports in clinical trials, worldwide voluntary reports of adverse events received for CERVARIX since market introduction (2007) are listed below. This list includes serious events or events which have suspected causal association to CERVARIX. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccination.

Immune System Disorders: Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema, erythema multiforme.

Nervous System Disorders: Syncope or vasovagal responses to injection (sometimes accompanied by tonic-clonic movements).

## 7 DRUG INTERACTIONS

### 7.1 Concomitant Vaccine Administration

There are no data to assess the concomitant use of CERVARIX with other vaccines.

Do not mix CERVARIX with any other vaccine in the same syringe or vial.

### 7.2 Hormonal Contraceptives

Among 7,693 subjects 15 through 25 years of age in Study 2 (CERVARIX, N = 3,821 or Hepatitis A Vaccine 720 EL.U., N = 3,872) who used hormonal contraceptives for a mean of 2.8 years, the observed efficacy of CERVARIX was similar to that observed among subjects who did not report use of hormonal contraceptives.

### 7.3 Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to CERVARIX *[see Use in Specific Populations (8.6)]*.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category B

Reproduction studies have been performed in rats at a dose approximately 47 times the human dose (on a mg/kg basis) and revealed no evidence of impaired fertility or harm to the fetus due to CERVARIX. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-Clinical Studies: An evaluation of the effect of CERVARIX on embryo-fetal, pre- and post-natal development was conducted using rats. One group of rats was administered CERVARIX 30 days prior to gestation and during the period of organogenesis (gestation days 6, 8, 11, and 15). A second group of rats was administered saline at 30 days prior to gestation followed by CERVARIX on days 6, 8, 11, and 15 of gestation. Two additional groups of rats received either saline or adjuvant following the same dosing regimen. CERVARIX was administered at 0.1 mL/rat/occasion (approximately 47-fold excess relative to the projected human dose on a mg/kg basis) by intramuscular injection. No adverse effects on mating, fertility, pregnancy, parturition, lactation, or embryo-fetal, pre- and post-natal development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis.

Clinical Studies: *Overall Outcomes:* In clinical studies, pregnancy testing was performed prior to each vaccine administration and vaccination was discontinued if a subject had a positive pregnancy test. In all clinical trials, subjects were instructed to take

precautions to avoid pregnancy until 2 months after the last vaccination. During pre-licensure clinical development, a total of 7,276 pregnancies were reported among 3,696 females receiving CERVARIX and 3,580 females receiving a control (Hepatitis A Vaccine 360 EL.U., Hepatitis A Vaccine 720 EL.U., or 500 mcg $Al(OH)_3$). The overall proportions of pregnancy outcomes were similar between treatment groups. The majority of women gave birth to normal infants (62.2% and 62.6% of recipients of CERVARIX and control, respectively). Other outcomes included spontaneous abortion (11.0% and 10.8% of recipients of CERVARIX and control, respectively), elective termination (5.8% and 6.1% of recipients of CERVARIX and control, respectively), abnormal infant other than congenital anomaly (2.8% and 3.2% of recipients of CERVARIX and control, respectively), and premature birth (2.0% and 1.7% of recipients of CERVARIX and control, respectively). Other outcomes (congenital anomaly, stillbirth, ectopic pregnancy, and therapeutic abortion) were reported less frequently in 0.1% to 0.8% of pregnancies in both groups.
*Outcomes Around Time of Vaccination:* Sub-analyses were conducted to describe pregnancy outcomes in 761 women [N = 396 for CERVARIX and N = 365 pooled control, HAV 360 EL.U., HAV 720 EL.U., and 500 mcg $Al(OH)_3$] who had their last menstrual period within 30 days prior to, or 45 days after a vaccine dose and for whom pregnancy outcome was known. The majority of women gave birth to normal infants (65.2% and 69.3% of recipients of CERVARIX and control, respectively). Spontaneous abortion was reported in a total of 11.7% of subjects (13.6% of recipients of CERVARIX and 9.6% of control recipients) and elective termination was reported in a total of 9.7% of subjects (9.9% of recipients of CERVARIX and 9.6% of control recipients). Abnormal infant other than congenital anomaly was reported in a total of 4.9% of subjects (5.1% of recipients of CERVARIX and 4.7% of control recipients) and premature birth was reported in a total of 2.5% of subjects (2.5% of both groups). Other outcomes (congenital anomaly, stillbirth, ectopic pregnancy, and therapeutic abortion) were reported in 0.3% to 1.8% of pregnancies among recipients of CERVARIX and in 0.3% to 1.4% of pregnancies among control recipients.
It is not known whether the observed numerical imbalance in spontaneous abortions in pregnancies which occurred around the time of vaccination is due to a vaccine-related effect.
Pregnancy Registry: Healthcare providers are encouraged to register pregnant women who inadvertently receive CERVARIX in the GlaxoSmithKline vaccination pregnancy registry by calling 1-888-452-9622.

**8.3 Nursing Mothers**
In non-clinical studies in rats, serological data suggest a transfer of anti-HPV-16 and anti-HPV-18 antibodies via milk during lactation in rats. Excretion of vaccine-induced antibodies in human milk has not been studied for CERVARIX. Because many drugs are excreted in human milk, caution should be exercised when CERVARIX is administered to a nursing woman.

**8.4 Pediatric Use**
Safety and effectiveness in pediatric patients younger than 10 years of age have not been established. The safety and effectiveness of CERVARIX have been evaluated in 1,193 subjects 10 through 14 years of age and 6,316 subjects 15 through 17 years of age. *[See Adverse Reactions (6.1) and Clinical Studies (14.5).]*

**8.5 Geriatric Use**
Clinical studies of CERVARIX did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. CERVARIX is not approved for use in subjects 65 years of age and older.

**8.6 Immunocompromised Individuals**
The immune response to CERVARIX may be diminished in immunocompromised individuals *[see Drug Interactions (7.3)]*.

**11 DESCRIPTION**
CERVARIX [Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant] is a non-infectious recombinant, AS04-adjuvanted vaccine that contains recombinant L1 protein, the major antigenic protein of the capsid, of oncogenic HPV types 16 and 18. The L1 proteins are produced in separate bioreactors using the recombinant Baculovirus expression vector system in a serum-free culture media composed of chemically-defined lipids, vitamins, amino acids, and mineral salts. Following replication of the L1 encoding recombinant Baculovirus in *Trichoplusia ni* insect cells, the L1 protein accumulates in the cytoplasm of the cells. The L1 proteins are released by cell disruption and purified by a series of chromatographic and filtration methods. Assembly of the L1 proteins into virus-like particles (VLPs) occurs at the end of the purification process. The purified, non-infectious VLPs are then adsorbed on to aluminum (as hydroxide salt). The adjuvant system, AS04, is composed of 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL) adsorbed on to aluminum (as hydroxide salt).
CERVARIX is prepared by combining the adsorbed VLPs of each HPV type together with the AS04 adjuvant system in sodium chloride, sodium dihydrogen phosphate dihydrate, and Water for Injection.
CERVARIX is a sterile suspension for intramuscular injection. Each 0.5-mL dose is formulated to contain 20 mcg of HPV type 16 L1 protein, 20 mcg of HPV type 18 L1 protein, 50 mcg of the 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL), and 0.5 mg of aluminum hydroxide. Each dose also contains 4.4 mg of sodium chloride and 0.624 mg of sodium dihydrogen phosphate dihydrate. Each dose may also contain residual amounts of insect cell and viral protein (<40 ng) and bacterial cell protein (<150 ng) from the manufacturing process. CERVARIX does not contain a preservative.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action
Animal studies suggest that the efficacy of L1 VLP vaccines may be mediated by the development of IgG neutralizing antibodies directed against HPV-L1 capsid proteins generated as a result of vaccination.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
CERVARIX has not been evaluated for its carcinogenic or mutagenic potential. Vaccination of female rats with CERVARIX, at doses shown to be significantly immunogenic in the rat, had no effect on fertility.

## 14 CLINICAL STUDIES
Cervical intraepithelial neoplasia (CIN) grade 2 and 3 lesions or cervical adenocarcinoma *in situ* (AIS) are the immediate and necessary precursors of squamous cell carcinoma and adenocarcinoma of the cervix, respectively. Their detection and removal has been shown to prevent cancer. Therefore, CIN2/3 and AIS (precancerous lesions) serve as surrogate markers for the prevention of cervical cancer. In clinical studies to evaluate the efficacy of CERVARIX, the endpoints were cases of CIN2/3 and AIS associated with HPV-16, HPV-18, and other oncogenic HPV types. Persistent infection with HPV-16 and HPV-18 that lasts for 12 months was also an endpoint.
The efficacy of CERVARIX to prevent histopathologically-confirmed CIN2/3 or AIS was assessed in 2 double-blind, randomized, controlled clinical studies that enrolled a total of 19,778 females 15 through 25 years of age.
Study 1 (HPV 001) enrolled women who were negative for oncogenic HPV DNA (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) in cervical samples, seronegative for HPV-16 and HPV-18 antibodies and had normal cytology. This represents a population presumed “naïve” without current HPV infection at the time of vaccination and without prior exposure to either HPV-16 or HPV-18. Subjects were enrolled in an extended follow-up study (Study 1 extension [HPV 007]) to evaluate the long-term efficacy, immunogenicity, and safety. These subjects have been followed for up to 6.4 years.
In Study 2 (HPV 008), women were vaccinated regardless of baseline HPV DNA status, serostatus or cytology. This study reflects a population of women naïve (without current infection and without prior exposure) or non-naïve (with current infection and/or with prior exposure) to HPV. Before vaccination, cervical samples were assessed for oncogenic HPV DNA (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) and serostatus of HPV-16 and HPV-18 antibodies.
In both studies, testing for oncogenic HPV types was conducted using $SPF_{10}$-$LiPA_{25}$ PCR to detect HPV DNA in archived biopsy samples.

### 14.1 Prophylactic Efficacy Against HPV Types 16 and 18
Study 2: A randomized, double-blind, controlled clinical trial was conducted in which 18,665 healthy females 15 through 25 years of age received CERVARIX or Hepatitis A Vaccine control on a 0-, 1-, and 6-month schedule. Among subjects, 54.8% of subjects were white, 31.5% Asian, 7.1% Hispanic, 3.7% black, and 2.9% were of other racial/ethnic groups.
In this study, women were randomized and vaccinated regardless of baseline HPV DNA status, serostatus or cytology. Women with HPV-16 or HPV-18 DNA present in baseline cervical samples (HPV DNA positive) at study entry were considered currently infected with that specific HPV type. If HPV DNA was not detected by PCR, women were considered HPV DNA negative. Additionally, cervical samples were assessed for cytologic abnormalities and serologic testing was performed for anti-HPV-16 and anti-HPV-18 serum antibodies at baseline. Women with anti-HPV serum antibodies present were considered to have prior exposure to HPV and characterized as seropositive. Women seropositive for HPV-16 or HPV-18 but DNA negative for that specific serotype were considered as having cleared a previous natural infection. Women without antibodies to HPV-16 and HPV-18 were characterized as seronegative. Before vaccination, 73.6% of subjects were naïve (without current infection [DNA negative] and without prior exposure [seronegative]) to HPV-16 and/or HPV-18.
Efficacy endpoints included histological evaluation of precancerous and dysplastic lesions (CIN grade 1, grade 2, or grade 3), and AIS. The mean follow-up after the first dose was approximately 39 months. Virological endpoints (HPV DNA in cervical samples detected by PCR) included 12-month persistent infection (defined as at least 2 positive specimens for the same HPV type over a minimum interval of 10 months).
The according to protocol (ATP) cohort for efficacy analyses for HPV-16 and/or HPV-18 included all subjects who received 3 doses of vaccine, for whom efficacy endpoint measures were available and who were HPV-16 and/or HPV-18 DNA negative and seronegative at baseline and HPV-16 and/or HPV-18 DNA negative at month 6 for the HPV type considered in the analysis. Case counting for the ATP cohort started on day 1 after the third dose of vaccine. This cohort included women who had normal or low-grade cytology (cytological abnormalities including atypical squamous cells of undetermined significance [ASC-US] or low grade squamous intraepithelial lesions [LSIL]) at baseline and excluded women with high-grade cytology.
The total vaccinated cohort (TVC) for each efficacy analysis included all subjects who received at least one dose of the vaccine, for whom efficacy endpoint measures were available, irrespective of their HPV DNA status, cytology, and serostatus at baseline. This cohort included women with or without current HPV infection and/or prior exposure. Case counting for the TVC started on day 1 after the first dose.

The TVC naïve is a subset of the TVC that had normal cytology, and were HPV DNA negative for 14 oncogenic HPV types and seronegative for HPV-16 and HPV-18 at baseline.
CERVARIX was efficacious in the prevention of precancerous lesions or AIS associated with HPV-16 or HPV-18 (Table 5).
Table 5. Efficacy of CERVARIX Against Histopathological Lesions Associated With HPV-16 or HPV-18 in Females 15 Through 25 Years of Age (According to Protocol Cohort[a]) (Study 2)

| | CERVARIX | | Control[b] | | % Efficacy (96.1% CI)[c] |
|---|---|---|---|---|---|
| | N | Number of Cases | N | Number of Cases | |
| CIN2/3 or AIS | 7,344 | 4 | 7,312 | 56 | 92.9 (79.9, 98.3) |
| CIN1/2/3 or AIS | 7,344 | 8 | 7,312 | 96 | 91.7 (82.4, 96.7) |

CI = Confidence Interval.

[a]Subjects (including women who had normal cytology, ASC-US, or LSIL at baseline) who received 3 doses of vaccine and were HPV DNA negative and seronegative at baseline and HPV DNA negative at month 6 for the corresponding HPV type (N). The mean follow-up was approximately 35 months.

[b]Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 mcg $Al(OH)_3$].

[c]The 96.1% confidence interval reflected in this final analysis results from statistical adjustment for the previously conducted interim analysis.
Since CIN3 or AIS represents a more immediate precursor to cervical cancer, cases of CIN3 or AIS associated with HPV-16 or HPV-18 were evaluated. In the ATP cohort, CERVARIX was efficacious in the prevention of CIN3 or AIS associated with HPV-16 or HPV-18 (vaccine efficacy = 80.0% [96.1% CI: 0.3, 98.1]).
Subjects who were already infected with one vaccine HPV type (16 or 18) prior to vaccination were protected from precancerous lesions or AIS and infection caused by the other vaccine HPV type.
Efficacy of CERVARIX against 12-month persistent infection with HPV-16 or HPV-18 was also evaluated. In the ATP cohort, CERVARIX reduced the incidence of 12-month persistent infection with HPV-16 and/or HPV-18 by 91.2% (96.1% CI: 85.9, 94.8).
Immune response following natural infection does not reliably confer protection against future infections. Among subjects who received 3 doses of CERVARIX and who were seropositive at baseline and DNA negative for HPV-16 or HPV-18 at baseline and month 6, CERVARIX reduced the incidence of 12-month persistent infection by 91.5% (96.1% CI: 64.0, 99.2%). However, the number of cases of CIN2/3 or AIS was too few to determine efficacy against histopathological endpoints in this population.
Study 1 and Study 1 Extension: In a second double-blind, randomized, controlled study (Study 1), the efficacy of CERVARIX in the prevention of HPV-16 or HPV-18 incident and persistent infections was compared with aluminum hydroxide control in 1,113 females 15 through 25 years of age. The population was naïve to current oncogenic HPV infection or prior exposure to HPV-16 and HPV-18 at the time of vaccination (total cohort). A total of 776 subjects were enrolled in the extended follow-up study (Study 1 Extension) to evaluate the long-term efficacy, immunogenicity, and safety of CERVARIX. These subjects have been followed for up to 6.4 years.
In Study 1 and Study 1 Extension, with up to 6.4 years of follow-up (mean 5.9 years), in naïve females 15 through 25 years of age, efficacy against CIN2/3 or AIS associated with HPV-16 or HPV-18 was 100% (98.67% CI: 28.4, 100). Efficacy against 12-month persistent infection with HPV-16 or HPV-18 was 100% (98.67% CI: 74.4, 100). The confidence interval reflected in this final analysis results from statistical adjustment for analyses previously conducted.

**14.2 Efficacy Against HPV Types 16 and 18, Regardless of Current Infection or Prior Exposure to HPV-16 or HPV-18**
Study 2: The study included women regardless of HPV DNA status (current infection) and serostatus (prior exposure) to vaccine types, HPV-16 or HPV-18 at baseline. Efficacy analyses included lesions arising among women regardless of baseline DNA status and serostatus, including HPV infections present at first vaccination and those from infections acquired after dose 1. In this population which includes naïve (without current infection and prior exposure) and non-naïve women, CERVARIX was efficacious in the prevention of precancerous lesions or AIS associated with HPV-16 or HPV-18 (Table 6).
However, among women HPV DNA positive regardless of serostatus at baseline, there was no clear evidence of efficacy against precancerous lesions or AIS associated with HPV-16 or HPV-18 (Table 6).
Table 6. Efficacy of CERVARIX Against Disease Associated With HPV-16 or HPV-18 in Females 15 Through 25 Years of Age, Regardless of Current or Prior Exposure to Vaccine HPV Types (Study 2)

| | CERVARIX | | Control | | % Efficacy (96.1% CI)[b] |
|---|---|---|---|---|---|
| | N | Number of Cases[a] | N | Number of Cases[a] | |
| **CIN1/2/3 or AIS** | | | | | |
| Prophylactic Efficacy[c] | 5,449 | 3 | 5,436 | 85 | 96.5 (89.0, 99.4) |

| | | | | | |
|---|---|---|---|---|---|
| HPV-16 or HPV-18 DNA Positive at Baseline[d] | 641 | 90 | 592 | 92 | -- |
| Regardless of Current Infection or Prior Exposure to HPV-16 or HPV-18[e] | 8,667 | 107 | 8,682 | 240 | 55.5[f] (43.2, 65.3) |
| **CIN2/3 or AIS** | | | | | |
| Prophylactic Efficacy[c] | 5,449 | 1 | 5,436 | 63 | 98.4 (90.4, 100) |
| HPV-16 or HPV-18 DNA Positive at Baseline[d] | 641 | 74 | 592 | 73 | -- |
| Regardless of Current Infection or Prior Exposure to HPV-16 or HPV-18[e] | 8,667 | 82 | 8,682 | 174 | 52.8[f] (37.5, 64.7) |
| **CIN3 or AIS** | | | | | |
| Prophylactic Efficacy[c] | 5,449 | 0 | 5,436 | 13 | 100 (64.7, 100) |
| HPV-16 or HPV-18 DNA Positive at Baseline[d] | 641 | 41 | 592 | 38 | -- |
| Regardless of Current Infection or Prior Exposure to HPV-16 or HPV-18[e] | 8,667 | 43 | 8,682 | 65 | 33.6[f] (-1.1, 56.9) |

CI = Confidence Interval.
Table does not include disease due to non-vaccine HPV types.

[a]Cases = Histopathological cases associated with HPV-16 and/or HPV-18.

[b]The 96.1% confidence interval reflected in this final analysis results from statistical adjustment for the previously conducted interim analysis.

[c]TVC naïve: includes all vaccinated subjects (who received at least one dose of vaccine) who had normal cytology, were HPV DNA negative for 14 oncogenic HPV types, and seronegative for HPV-16 and HPV-18 at baseline (N). Case counting started on day 1 after the first dose.

[d]TVC subset: includes all vaccinated subjects (who received at least one dose of vaccine) who were HPV DNA positive for HPV-16 or HPV-18 irrespective of serostatus at baseline (N). Case counting started on day 1 after the first dose.

[e]TVC: includes all vaccinated subjects (who received at least one dose of vaccine) irrespective of HPV DNA status and serostatus at baseline (N). Case counting started on day 1 after the first dose.

[f]Observed vaccine efficacy includes the prophylactic efficacy of CERVARIX and the impact of CERVARIX on the course of infections present at first vaccination.

**14.3 Efficacy Against Cervical Disease Irrespective of HPV Type, Regardless of Current or Prior Infection with Vaccine or Non-Vaccine HPV Types**

Study 2: The impact of CERVARIX against the overall burden of HPV-related cervical disease results from a combination of prophylactic efficacy against, and disease contribution of, HPV-16, HPV-18, and non-vaccine HPV types.

In the population naïve to oncogenic HPV (TVC naïve), CERVARIX reduced the overall incidence of CIN1/2/3 or AIS, CIN2/3 or AIS, and CIN3 or AIS regardless of the HPV DNA type in the lesion (Table 7). In the population of women naïve and non-naïve (TVC), vaccine efficacy against CIN1/2/3 or AIS, CIN2/3 or AIS, and CIN3 or AIS was demonstrated in all women regardless of HPV DNA type in the lesion (Table 7).

Table 7. Efficacy of CERVARIX in Prevention of CIN or AIS Irrespective of Any HPV Type in Females 15 Through 25 Years of Age, Regardless of Current or Prior Infection with Vaccine or Non-Vaccine Types (Study 2)

| | **CERVARIX** | | **Control** | | |
|---|---|---|---|---|---|
| | **N** | **Number of Cases** | **N** | **Number of Cases** | **% Efficacy (96.1% CI)[a]** |
| **CIN1/2/3 or AIS** | | | | | |
| Prophylactic Efficacy[b] | 5,449 | 106 | 5,436 | 211 | 50.1 (35.9, 61.4) |
| Irrespective of HPV DNA at Baseline[c] | 8,667 | 451 | 8,682 | 577 | 21.7 (10.7, 31.4) |
| **CIN2/3 or AIS** | | | | | |
| Prophylactic Efficacy[b] | 5,449 | 33 | 5,436 | 110 | 70.2 (54.7, 80.9) |

| | | | | | |
|---|---|---|---|---|---|
| Irrespective of HPV DNA at Baseline[c] | 8,667 | 224 | 8,682 | 322 | 30.4 (16.4, 42.1) |
| **CIN3 or AIS** | | | | | |
| Prophylactic Efficacy[b] | 5,449 | 3 | 5,436 | 23 | 87.0 (54.9, 97.7) |
| Irrespective of HPV DNA at Baseline[c] | 8,667 | 77 | 8,682 | 116 | 33.4 (9.1, 51.5) |

CI = Confidence Interval.

[a] The 96.1% confidence interval reflected in this final analysis results from statistical adjustment for the previously conducted interim analysis.

[b]TVC naïve: includes all vaccinated subjects (who received at least one dose of vaccine) who had normal cytology, were HPV DNA negative for 14 oncogenic HPV types (including HPV-16 and HPV-18), and seronegative for HPV-16 and HPV-18 at baseline (N). Case counting started on day 1 after the first dose.

[c] TVC: includes all vaccinated subjects (who received at least one dose of vaccine) irrespective of HPV DNA status and serostatus at baseline (N). Case counting started on day 1 after the first dose.

In exploratory analyses, CERVARIX reduced definitive cervical therapy procedures (includes loop electrosurgical excision procedure [LEEP], cold-knife Cone, and laser procedures) by 24.7% (96.1% CI: 7.4, 38.9) in the TVC and by 68.8% (96.1% CI: 50.0, 81.2) in the TVC naïve.

To assess reductions in disease caused by non-vaccine HPV types, two analyses were conducted combining 12 non-vaccine oncogenic HPV types, including and excluding lesions in which HPV-16 or HPV-18 were also detected. In these analyses, among females who received 3 doses of CERVARIX and were DNA negative for the specific HPV type at baseline and month 6, CERVARIX reduced the incidence of CIN2/3 or AIS by 54.0% (96.1% CI: 34.0, 68.4) and 37.4% (96.1% CI: 7.4, 58.2), respectively.

Post-hoc analyses, adjusted for multiplicity, were conducted to assess the impact of CERVARIX on CIN2/3 or AIS due to specific non-vaccine HPV types. The ATP cohort for these analyses included all subjects irrespective of serostatus who received 3 doses of CERVARIX and were DNA negative for the specific HPV type at baseline and month 6. These post-hoc analyses were also conducted in the TVC naïve population. In analyses including lesions in which HPV-16 or HPV-18 were also detected, vaccine efficacy in prevention of CIN2/3 or AIS associated with HPV-31 was 92.0% (99.7% CI: 49.0, 99.8) and 100% (99.7% CI: 62.3, 100), respectively. In analyses excluding lesions in which HPV-16 or HPV-18 were detected, vaccine efficacy in prevention of CIN2/3 or AIS associated with HPV-31 was 89.4% (99.7% CI: 29.0, 99.7) and 100% (99.7% CI: 36.3, 100), respectively.

**14.4 Immunogenicity**

The minimum anti-HPV titer that confers protective efficacy has not been determined.

The antibody response to HPV-16 and HPV-18 was measured using a type-specific binding ELISA (developed by GlaxoSmithKline) and a pseudovirion-based neutralization assay (PBNA). In a subset of subjects tested for HPV-16 and HPV-18, the ELISA has been shown to correlate with the PBNA. The scales for these assays are unique to each HPV type and each assay, thus, comparison between HPV types or assays is not appropriate.

Duration of Immune Response: The duration of immunity following a complete schedule of immunization with CERVARIX has not been established. In Study 1 and Study 1 Extension, the immune response against HPV-16 and HPV-18 was evaluated for up to 76 months post-dose 1, in females 15 through 25 years of age. Vaccine-induced geometric mean titers (GMTs) for both HPV-16 and HPV-18 peaked at month 7 and thereafter reached a plateau that was sustained from month 18 up to month 76. At all timepoints, >98% of subjects were seropositive for both HPV-16 (≥8 EL.U./mL, the limit of detection) and HPV-18 (≥7 EL.U./mL, the limit of detection) by ELISA.

In Study 2, GMTs for ELISA and PBNA one month post-dose 3 were measured (Table 8). The ATP cohort for immunogenicity included all evaluable subjects for whom data concerning immunogenicity endpoint measures were available. These included subjects for whom assay results were available for antibodies against at least one vaccine type. Subjects who acquired either HPV-16 or HPV-18 infection during the trial were excluded. Of subjects seronegative at baseline, 99.5% were seropositive for anti-HPV-16 and anti-HPV-18 antibodies at month 7 post-vaccination.

Table 8. Summary of Anti-HPV Geometric Mean Titers (GMTs) for HPV-16 and HPV-18 at Month 7 for Initially Seronegative Females 15 Through 25 Years of Age (According to Protocol Cohort for Immunogenicity[a]) (Study 2)

| **Antibody Assay** | **N** | **CERVARIX GMT (95% CI)** | **N** | **Control GMT (95% CI)** |
|---|---|---|---|---|
| **ELISA[b] (EL.U./mL)** | | | | |
| Anti-HPV-16 | 861 | 9,206.4 (8,607.2, 9,847.2) | 738 | 4.4 (4.2, 4.6) |
| Anti-HPV-18 | 924 | 4,744.6 (4,454.1, 5,053.9) | 769 | 3.8 (3.6, 3.9) |
| **PBNA[c] ($ED_{50}$)** | | | | |

| | | | | |
|---|---|---|---|---|
| Anti-HPV-16 | 46 | 27,364.8 (19,780.1, 37,857.9) | 44 | 20.0 (20.0, 20.0) |
| Anti-HPV-18 | 46 | 9,052 (6,851.8, 11,960.5) | 44 | 20.0 (20.0, 20.0) |

[a]Subjects who received 3 doses of vaccine for whom assay results were available for at least one post-vaccination antibody measurement (N). Subjects who acquired either HPV-16 or HPV-18 infection during the study were excluded.

[b]Enzyme linked immunosorbent assay (assay cut-off 8 EL.U./mL for anti-HPV-16 antibody and 7 EL.U./mL for anti-HPV-18 antibody).

[c]Pseudovirion-based neutralization assay (assay cut-off 40 $ED_{50}$ for both anti-HPV-16 antibody and anti-HPV-18 antibody).

**14.5 Bridging of Efficacy from Women to Adolescent Girls**

The immunogenicity of CERVARIX was evaluated in 2 clinical studies involving 1,193 girls 10 through 14 years of age who received CERVARIX.

Study 3 (HPV 013) was a double-blind, randomized, controlled study in which 1,035 subjects received CERVARIX and 1,032 subjects received a Hepatitis A Vaccine 360 EL.U. as the control vaccine with a subset of subjects evaluated for immunogenicity. All initially seronegative subjects in the group who received CERVARIX were seropositive after vaccination, i.e., had levels of antibody greater than the limit of detection of the assay to both HPV-16 (≥8 EL.U./mL) and HPV-18 (≥7 EL.U./mL) antigens. The GMTs for anti-HPV-16 and anti-HPV-18 antibodies in initially seronegative subjects are presented in Table 9.

Table 9. Geometric Mean Titers (GMTs) at Months 7 and 18 for Initially Seronegative Females 10 Through 14 Years of Age (According To Protocol Cohort for Immunogenicity[a]) (Study 3)

| | **Anti-HPV-16 Antibodies GMT EL.U./mL (95% CI)** | | | **Anti-HPV-18 Antibodies GMT EL.U./mL (95% CI)** | | |
|---|---|---|---|---|---|---|
| **Age Group** | **N** | **Month 7** | **Month 18** | **N** | **Month 7** | **Month 18** |
| 10-14 years of age | 556-619 | 19,882.0 (18,626.7, 21,221.9) | 3,888.8 (3,605.0, 4,195.0) | 562-628 | 8,262.0 (7,725.0, 8,836.2) | 1,539.4 (1,418.8, 1,670.3) |

[a]Subjects who received 3 doses of vaccine for whom assay results were available for at least one post-vaccination antibody measurement (N).

In Study 4 (HPV 012), the immunogenicity of CERVARIX administered to girls 10 through 14 years of age was compared to that in females 15 through 25 years of age. The immune response in girls 10 through 14 years of age measured one month post-dose 3 was non-inferior to that seen in females 15 through 25 years of age for both HPV-16 and HPV-18 antigens (Table 10).

Table 10. Geometric Mean Titers (GMTs) and Seropositivity Rates at Month 7 for Initially Seronegative Females 10 Through 14 Years of Age Compared to 15 Through 25 Years of Age (According To Protocol Cohort for Immunogenicity[a]) (Study 4)

| | **10-14 Years of Age** | | | **15-25 Years of Age** | | |
|---|---|---|---|---|---|---|
| **Antibody Assay** | **N** | **GMT[b] EL.U./mL (95% CI)** | **Seropositivity Rate[c] %** | **N** | **GMT[b] EL.U./mL (95% CI)** | **Seropositivity Rate[c] %** |
| Anti-HPV-16 | 143 | 17,272.5 (15,117.9, 19,734.1) | 100 | 118 | 7,438.9 (6,324.6, 8,749.6) | 100 |
| Anti-HPV-18 | 141 | 6,863.8 (5,976.3, 7,883.0) | 100 | 116 | 3,070.1 (2,600.0, 3,625.4) | 100 |

[a]Subjects who received 3 doses of vaccine for whom assay results were available for at least one post-vaccination antibody measurement (N).

[b]Non-inferiority based on the upper limit of the 2-sided 95% CI for the GMT ratio (15-25 year olds/10-14 year olds) was <2.

[c]Non-inferiority based on the upper limit of the 2-sided 95% CI for the difference between the seropositivity rates for 10-14 year olds and 15-25 year olds was <10%.

Based on these immunogenicity data, the efficacy of CERVARIX is inferred in girls 10 through 14 years of age.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

CERVARIX is available in 0.5-mL single-dose vials and prefilled TIP-LOK syringes.

Single-Dose Vials

NDC 58160-830-11 (package of 10)

Single-Dose Prefilled Disposable TIP-LOK Syringes (packaged without needles)

NDC 58160-830-32 (package of 1)

NDC 58160-830-46 (package of 5)
Store refrigerated between 2º and 8ºC (36º and 46ºF). Do not freeze. Discard if the vaccine has been frozen. Upon storage, a fine, white deposit with a clear, colorless supernatant may be observed. This does not constitute a sign of deterioration.

**17 PATIENT COUNSELING INFORMATION**
Provide the Vaccine Information Statements prior to immunization. This is required by the National Childhood Vaccine Injury Act of 1986 and are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).
Inform the patient, parent, or guardian:

- Vaccination does not substitute for routine cervical cancer screening. Women who receive CERVARIX should continue to undergo cervical cancer screening per standard of care.
- CERVARIX does not protect against disease from HPV types to which a woman has previously been exposed through sexual activity.
- Since syncope has been reported following vaccination in young females, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended.
- Information regarding potential benefits and risks associated with vaccination.
- Report any adverse events to their healthcare provider.
- Safety has not been established in pregnant women. CERVARIX is not recommended for use in pregnant women or women planning to become pregnant during the vaccination course. Register women who receive CERVARIX while pregnant in the pregnancy registry by calling 1-888-452-9622.

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Research Triangle Park, NC 27709

**Principal Display Panel**
NDC 58160-830-11
CERVARIX®
Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant
10 x 0.5 mL Single-Dose Vials
Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if frozen.
Each 0.5-mL dose contains 20 mcg of human papillomavirus type 16 L1 protein; 20 mcg of human papillomavirus type 18 L1 protein; 50 mcg of 3-*O*-deacyl-4'-monophosphoryl lipid A (MPL), and 0.5 mg of aluminum hydroxide. The adjuvant system, AS04, is composted of MPL absorbed on to aluminum (as hydroxide salt).
Contains no preservative.
Do not dilute; shake well before using. For intramuscular administration only.
Dosage: 0.5 mL equals one dose. The vaccination course consists of 3 doses administered at 0, 1 and 6 months.
See complete prescribing information for additional details.
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10 x 0.5 mL Single-Dose Vials
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Vaccine, Recombinant
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Contains no preservative.
Do not dilute; shake well before using. For intramuscular administration only.
Dosage: 0.5 mL equals one dose. The vaccination course consists of 3 doses administered at 0, 1, and 6 months.
See complete prescribing information for additional details.
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